Hepatitis C: A New Era

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KEYWORDS

• Hepatitis C • Hepatic fibrosis • HCV • Direct-acting antivirals

KEY POINTS

- Hepatitis C virus (HCV) is a common but underdiagnosed infection that affects at least 2 million Americans, about half of whom are unaware that they are infected.
- Given its often asymptomatic initial course, screening for HCV in those with risk factors is of utmost importance in the primary care setting.
- HCV causes many hepatic and extrahepatic complications, including cirrhosis, hepatocellular carcinoma, and death.
- With the advent of direct-acting antivirals, treatment of HCV is more successful than ever.

EPIDEMIOLOGY

The hepatitis C virus (HCV) is a small, single-stranded RNA virus in the Flaviviridae family with 6 genotypes and a propensity to cause chronic infection.[1] Approximately 2.7 to 7.1 million Americans have chronic hepatitis C.[2,3] It is estimated that 16,000 to 75,000 deaths yearly are attributed to HCV, and more Americans die from HCV than any other infectious cause (including HIV, tuberculosis, and pneumococcal disease).[4] Hepatitis C is also a costly disease, and costs are increasing. The number of admissions in the United States related to HCV tripled from the time period of 2004 to 2005 to 2010 to 2011.[5] Costs of US hospitalizations have also tripled in that same period, from $0.9 billion to $3.5 billion. The financial burden is shifting from private insurers to Medicare as the baby-boomer generation ages.

PATHOPHYSIOLOGY

Transmission

HCV is primarily transmitted through percutaneous blood exposure, and injection drug use accounts for at least 60% of cases in the United States.[6] The prevalence of HCV

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among persons who inject drugs is approximately 50%.[7] Although sexual transmission is possible, it is generally inefficient except in cases of HIV coinfection or in men who have sex with men (MSM).[6]

Acute Phase

After contracting the virus, the incubation period lasts 2 to 26 weeks. The acute phase of infection lasts 1 to 3 weeks and is rarely symptomatic enough to be clinically evident. Although possible, hepatitis with acute liver failure is very rare in the acute setting.[8] At this time, however, HCV RNA is elevated and detectable, and serum transaminases are also elevated. Some individuals mount a robust immune response with T cells and thus clear the virus. Of patients infected, 20% to 50% will clear the virus and recover from the acute infection.[1] However, 50% to 80% are unable to clear the infection because the virus has several mechanisms to elude the immune system; these patients develop chronic hepatitis C.

Chronic Phase

The chronic phase of HCV infection is variable.[9] HCV directly impacts the liver by effectively creating an environment of low-grade hepatic inflammation. This inflammatory environment stimulates hepatic stellate cells to transform into myofibroblasts, thus leading to the production and accumulation of matrix proteins within the liver.[10] Some patients exhibit a mild progression of hepatitis, where inflammation is only seen in the portal tracts so that the liver architecture is maintained properly. Even in the mildest forms, hepatocyte apoptosis will still occur. Bridging necrosis and fibrosis between the portal tracts and hepatic veins is seen in advancing disease.

The result of ongoing hepatocyte destruction and fibrosis is cirrhosis. Given the largely asymptomatic initial course of acute and early chronic HCV and resulting delayed clinical diagnosis, it is difficult to determine the typical time frame for developing HCV-related cirrhosis. The overall risk appears to be about 15%, although cirrhosis can take up to 20 years after infection to become clinically apparent.[11,12] Once an HCV-infected patient becomes cirrhotic, the risk of developing liver failure, hepatocellular carcinoma (HCC), or liver-related death is about 3% for each outcome annually.[13] HCV is the underlying cause of one-half of liver disease cases in the United States.[9] Of patients with end-stage liver disease waiting for a liver transplant, 35% have HCV.[14]

DIAGNOSIS

Risk Assessment

Approximately half of those infected with HCV are unaware that they have the virus. Therefore, a major part of HCV diagnosis is the screening of asymptomatic but at-risk individuals. Risk factors include the following:

- Injection or intranasal drug use
- Unregulated tattoos
- Needle stick injuries
- Long-term hemodialysis
- HCV-infected mother
- Blood transfusion or organ transplant before 1992
- Incarceration
- Concomitant HIV infection

In addition, given exposures and behaviors within this particular birth cohort and a 5 times greater prevalence than other populations, all asymptomatic patients born between 1945 and 1965 should be offered one-time HCV screening. Testing should also be completed in patients with unexplained liver dysfunction or persistently elevated transaminase levels.[15]

Choice of Screening Test

There are traditionally 2 stages to diagnosing HCV infection: an initial antibody screen followed by a confirmatory virologic assay. Two-step testing is necessary because antibody tests are insensitive in the early stages of infection and lack the ability to differentiate acute disease from chronic or recovered states. In addition, false positive antibody results can occur in low-titer samples.[6]

The presence of circulating anti-HCV antibodies is detected using either enzyme immunoassay (EIA; or enzyme-linked immunosorbent assay) or chemiluminescence assay (CLIA). Clinically, these serum assays are ordered as a "Hepatitis C Antibody Test" or "Anti-HCV Antibody"; they are 97% to 98% sensitive and specific.[6] In low-resource settings, rapid diagnostic tests (RDTs) appear to increase diagnosis of high-risk individuals and should be considered for initial HCV antibody testing.[16] RDTs are available as either blood or oral fluid–based studies, have comparable sensitivity and specificity (83%–100% and 99%–100%, respectively), require little laboratory infrastructure, and are less costly than their EIA and CLIA counterparts.[17] Although sensitivity and specificity of antibody tests are high in the general population, immunocompromised patients (eg, those with HIV or on hemodialysis) may have an impaired antibody response and thus false negative results (specificity 65%–89%).[6,18] **Table 1** summarizes the best initial screening tests to order in a variety of clinical scenarios.

Approach to the Positive Antibody

In patients with positive antibody testing, a follow-up virologic study should be ordered to determine the presence or absence of current hepatitis C infection. The confirmatory study of choice is the HCV RNA test, which can be ordered as either a quantitative or a qualitative measure; both methods use nucleic acid testing (NAT) and are reliable measures of viral replication. HCV RNA is detectable in serum 1 to 2 weeks after an initial infection. Although quantitative tests are more revealing in that they report a standard measure of international units per milliliter (also known as a "viral load"), the qualitative study has traditionally had the advantage of detecting the presence of circulating virus at lower levels than many of its quantitative counterparts.[19] However, it is currently recommended that either measure of HCV RNA (whether qualitative or quantitative) must have a threshold of detection of 25 IU/mL or lower in order to be clinically useful.[15]

Although not currently available in every practice setting, the HCV core antigen test could be considered over HCV RNA testing in some clinical scenarios. Core antigen testing nears 100% specificity and is less labor intensive with a lower risk of laboratory contamination than NAT technology.[6] In very high-prevalence settings, it could also be used as a one-step diagnostic approach.[17] However, there is lacking evidence to recommend one-step core antigen testing over 2-step or HCV RNA testing in most situations. **Fig. 1** visually summarizes the stepwise process to diagnosing hepatitis C.

FIBROSIS STAGING

METAVIR System

Once HCV infection has been identified, it is important for prognostic and therapeutic purposes to evaluate the extent of fibrosis that has occurred in the liver. Clinically,

Table 1
Summary of screening recommendations for hepatitis C virus infection

Risk Factor	Preferred Initial Screening Test	Need for Ongoing Assessment/ Screening?	Notes
Injection or intranasal drug use	HCV antibody	Yes, if risk behavior continues	Screen even if patient has only used once
Unregulated tattoo recipient	HCV antibody and HCV RNA	Yes, if ongoing risk/exposure	Tattoos received in state-regulated parlors should be safe
Incarceration	HCV antibody	No (once only unless other risk factors)	Risk includes current or past incarceration
Blood transfusion or organ transplant before 1992 or receipt of clotting factors before 1987	HCV antibody	No (once only)	Also test in those who were notified following a transfusion that the donor tested positive for HCV
US-born between 1945 and 1965	HCV antibody	No (once only), unless other ongoing risk factor	75% of those with the virus are in this birth cohort
Long-term hemodialysis (ever)	HCV antibody	No	HCV Ab not reliably detectable given immunocompromise
HIV infection	HCV antibody AND HCV RNA	Annually in HIV-positive MSM	HCV Ab not reliably detectable given immunocompromise
Children born to HCV-infected mothers	HCV RNA twice between 2 and 6 mo of age OR HCV Ab after 15 mo of age	No (see guidelines)	Per National Institutes of Health Consensus Guidelines

Adapted from AASLD/IDSA HCV Guidance Panel. Hepatitis C guidance: AASLD-IDSA recommendations for testing, managing, and treating adults infected with hepatitis C virus. Hepatology 2015;62(30):933–4; with permission.

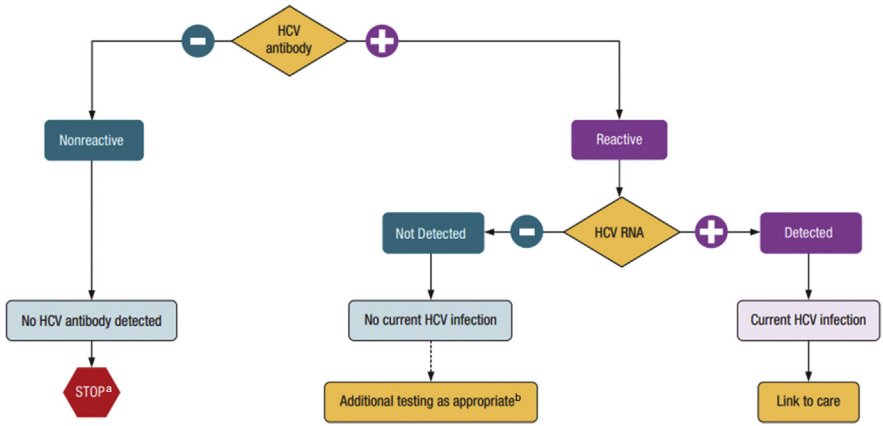

Fig. 1. Recommended testing sequence for identification of current HCV infection. [a] For persons who might have been exposed to HCV within the past 6 months, testing for HCV RNA or follow-up testing for HCV antibody is recommended. For persons who are immunocompromised, testing for HCV RNA can be considered. [b] To differentiate past, resolved HCV infection from biologic false positivity for HCV antibody, testing with another HCV antibody assay can be considered. Repeat HCV RNA testing if the person tested is suspected to have had HCV exposure within the past 6 months or has clinical evidence of HCV disease, or if there is concern regarding the handling or storage of the test specimen. (*From* Centers for Disease Control and Prevention (CDC). Testing for HCV infection: an update of guidance for clinicians and laboratorians. MMWR Morb Mortal Wkly Rep 2013;62:362–5; with permission.)

hepatic fibrosis can be staged using various scoring methods, the best studied of which is the METAVIR system. Using this system, a patient's fibrosis score ranges along a spectrum from F0 (no fibrosis) to F4 (cirrhosis). F1, F2, and F3 represent interval stages preceding cirrhosis but with progressively increasing bridging septum formation.[20] A METAVIR score is determined by 1 of 3 techniques, each with similar performance: liver biopsy, serum assay, or ultrasound-based testing.[21]

Liver Biopsy

Liver biopsy has been the historical gold standard of fibrosis assessment because it provides information regarding other predictive and prognostic processes, including inflammation, steatosis, and necrosis. However, biopsy is limited by its invasive risk, contraindications, and cost; additionally, it is fraught with potential sampling error in that a small specimen may not accurately represent the liver as a whole.[22] As other means of assessing fibrosis have become available and current treatments hold fewer risks and better outcomes, liver biopsies have become less standard in the management of hepatitis C.

Serum Testing for Fibrosis

There are several available serum tests for fibrosis, broadly classified as either direct or indirect. Indirect tests comprise simple serum measurements reflecting portal hypertension, liver dysfunction, or inflammation. They can be combined to produce diagnostic panels such as the aspartate aminotransferase (AST) to platelet ratio index (APRI), calculated as follows: (AST/upper limit of normal for sampling laboratory test)

× 100/platelet count. The higher the resulting number, the more likely the presence of significant fibrosis.

Direct tests measure markers of collagen synthesis or degradation, the most validated of which is hyaluronic acid. Several available tests combine direct and indirect markers, often also taking into account patient age and sex, and provide a resulting METAVIR score. Of these, the most widely validated and available in the United States is the FibroSURE test.[22] Although APRI and FibroSURE perform similarly, the former is less predictive because of the possibility of extrahepatic causes of thrombocytopenia or transaminitis, and the latter is significantly more costly.[23]

Imaging for Fibrosis

Imaging techniques for the measurement of fibrosis include ultrasound, computed tomography, and MRI-based methods. The most broadly used is transient elastography (TE; FibroScan), which uses an ultrasound transducer along with a vibrating device that releases low-frequency shearing waves; the speed of wave transmission is directly related to liver stiffness. Although this is a more accurate measure of cirrhosis than fibrosis, it can be used for either. Testing accuracy is further limited by several factors, including the presence of obesity, ascites, and acute hepatic inflammation. Magnetic resonance elastography is clinically superior to TE in that it visualizes the entirety of the liver with fewer patient-factor limitations, but is more cost-prohibitive and generally less available in many testing centers.[22]

CLINICAL MANIFESTATIONS

Hepatic Manifestations

Cirrhosis

Ongoing liver fibrosis leads to cirrhosis, which manifests clinically in a variety of ways, including but not limited to the following:

- Esophageal varices
- Hepatomegaly
- Ascites
- Gynecomastia
- Infertility and anovulation
- Spider angiomas
- Palmar erythema[24]

Cirrhosis is also reflected in several typical laboratory findings, including pancytopenia, transaminitis, increased bilirubin, and dilutional hyponatremia.

Hepatocellular carcinoma

HCC is the most common primary liver malignancy and the ninth leading cause of cancer-related death in the United States. Cirrhosis of any origin is a risk factor for its development. The cycle of cell death and regeneration seen in chronic hepatitis C can increase the risk of accumulated mutations in hepatocyte DNA, malignantly transform the cells, and increase the risk of HCC.[9] Alcohol consumption, diabetes mellitus, and obesity appear to confer additional risk. HCC develops almost exclusively in the cirrhotic liver, although up to 8% of cases occur in severe fibrosis.[25]

There are unfortunately no pathognomonic symptoms of HCC and, given the overlap with cirrhosis, any potential clinical manifestations are typically already present. These limiting factors often leads to late-stage diagnosis of HCC, at which point no available treatment can increase survival. If discovered at an early enough

stage, radiation and chemotherapy are possible treatment options, but the only available curative treatments for HCC are surgical resection and orthotopic liver transplant.[25]

Extrahepatic Manifestations

Although primarily affecting the liver, HCV should be considered a systemic disease in that it leads to the development of immunologic, autoimmune, and viral phenomena throughout the body.[26] An estimated 40% to 74% of HCV patients will develop at least one extrahepatic manifestation throughout the course of their illness, leading to increased treatment cost and overall economic burden.[26,27]

Those conditions with the strongest HCV association include the following:

- Mixed cryoglobulinemia
- B-cell non-Hodgkin lymphoma[28]

Other manifestations include the following:

- Lichen planus
- Type 2 diabetes mellitus
- Membranoproliferative glomerulonephritis
- Porphyria cutanea tarda
- Rheumatoid-like arthritis
- Depression[27,28]

Successful treatment does appear to improve many systemic manifestations, and in addition, decreases mortality.[28]

TREATMENT

Goals of Treatment

The ultimate goal of HCV treatment is to eradicate the infection. Successful eradication is defined as having an undetectable viral load 12 weeks following treatment completion, also termed sustained virologic response (SVR). SVR confers a 97% to 100% chance of being HCV RNA negative long term and can therefore be considered a "cure."[29] Once SVR is achieved, patients will continue to have a detectable HCV antibody, but this does not imply immunity.

Secondary goals of HCV treatment include reducing clinical sequelae as well as decreasing future transmission risk and prevalence. Achieving SVR decreases the risk of developing chronic HCV, end-stage liver disease, HCC, and death. Therefore, treatment is especially important in cases of compensated cirrhosis, advanced fibrosis staging, severe extrahepatic HCV, and history of liver transplant.[15]

Nonpharmacologic therapy

Lifestyle changes are recommended to help reduce consequences of HCV[30]; this includes avoiding alcohol use in order to decrease disease progression. Patients should also eat a balanced diet and exercise regularly to obtain or maintain a normal weight, thus reducing the risk of concomitant nonalcoholic fatty liver disease or nonalcoholic steatohepatitis. Tobacco use can also contribute to disease progression, and a study comparing daily with occasional cannabis use in the setting of HCV infection showed higher rates of moderate to severe fibrosis in the daily users. Therefore, cessation of both tobacco and cannabis should be encouraged.[31] HCV patients should additionally be vaccinated against hepatitis A and B, and cirrhotic patients should receive

pneumonia vaccination.[32] Last, patients should be educated on how to minimize HCV transmission by avoiding the following[33]:

- Sharing or reuse of needles, syringes, and other injectable devices
- Sharing personal items that may be infected (razor, toothbrush, nail-clippers)
- Acquiring tattoos or piercings from an unlicensed facility

Pharmacologic therapy

Interferon regimens After the discovery of HCV in 1989, interferon (IFN) was for several years the only HCV treatment regimen available and remained a staple of its management until 2012. It was originally used to treat hepatitis B before its use to treat HCV. Unfortunately, IFN was limited by poor efficacy with SVR rates of 15% to 20%.[34] In addition, IFN was associated with several intolerable side effects, such as neutropenia, myalgia, influenza-like symptoms, autoimmune disorders, depression, or other neuropsychiatric disturbances. These limiting clinical factors led to frequent discontinuation of IFN therapy by patients, which also contributed to poor SVR rates.

Ribavirin In the late 1990s, ribavirin was added to IFN regimens and improved SVR rates significantly to 38% to 56%.[34] Ribavirin is a nucleoside analogue, but the mechanism of its augmenting effects is not well known. This medication requires close therapeutic monitoring because it can cause hemolytic anemia. It can also worsen cardiac disease, leading to myocardial infarction. Ribavirin cannot be used in pregnant women because it is a pregnancy category X medication. When used in women of childbearing age, 2 forms of contraception are required during treatment and for 6 months after. Although use of ribavirin is diminishing, it is still used in combination with direct-acting antivirals (DAAs) in certain patients, such as those previously exposed to treatment or those with cirrhosis.[35]

Direct-acting antivirals In 2013, the first DAA was approved, drastically changing the landscape of HCV treatment. DAAs are now recommended for first-line management. They have improved SVR rates to 95% to 100% and have created the option of IFN-free regimens.[36] Although these medications are all broadly categorized as DAAs, they do have different mechanisms of action. The first 2 brought to market were protease inhibitors, boceprevir and telaprevir. Both still required use with IFN and ribavirin and had a limiting side-effect profile, which led to discontinuation of these medications in the US market when more tolerable agents were made available. The remaining DAAs affect HCV replication by targeting crucial viral proteins that inhibit the replication process. Specific types of available DAAs include HCV serine proteases, nonstructural protein inhibitors, nucleotide analogue inhibitors, nucleoside analogue inhibitors, and nonnucleoside inhibitors the remaining DAAs target crucial viral proteins and thus inhibit the HCV replication process.[34]

Each DAA is active against certain genotypes of the virus. The most common genotypes in the United States are 1, 2, and 3 and account for 97% of cases.[1] When selecting a DAA, patient genotype, cost, potential drug interactions, and side effects should be considered (**Table 2**). As DAAs are a new, innovative treatment of HCV, they have a high market value, ranging from $60,000 to 90,000 for one course of treatment.[34] However, DAAs have a more tolerable side-effect profile, fewer drug interactions, and an easier dosing schedule than IFN or ribavirin. These factors have allowed the management of HCV to occur in a primary care setting in some cases, as opposed to specialty environments only.

Table 2
Directing-acting antiviral medication chart

Medication, Brand (Generic)[a]	Genotypes Covered	Side Effects	Contraindications	Duration of Therapy, wk	SVR Rates, %	Other
Epclusa[37] (sofosbuvir/velpatasvir)	1, 2, 3, 4, 5, 6	Headache, fatigue	Coadministration with amiodarone	12	97–100	Used with ribavirin in decompensated cirrhosis
Zepatier[38] (elbasvir/grazoprevir)	1, 4	Headache, fatigue, and nausea	Moderate-severe hepatic impairment, use with OATP inhibitors/CYP3A inducers[b]/efavirenz	12–16	95–100	Used with ribavirin in treatment, experienced or NS5A polymorphisms
Daklinza[39] (daclatasvir)	1, 3	Headache, fatigue	CYP3A inducers[b]	12	82–100	Used with sofosbuvir; used with ribavirin in decompensated cirrhosis
Technivie[40] (ombitasvir/paritaprevir/ritonavir)	4	Asthenia, fatigue, nausea, insomnia	Moderate-severe hepatic impairment, CYP3A inducers,[b] sensitivity to ritonavir or ribavirin, ethinyl estradiol	12	91–100	Used with ribavirin
Viekira Pak[41] (ombitasvir/paritaprevir/ritonavir + dasabuvir)	1	Fatigue, nausea, pruritus, insomnia, asthenia	Severe hepatic impairment, CYP3A inducers,[b] CYP2C8 strong inducers and inhibitors, ethinylestradiol	12–24	95–100	Used with ribavirin in decompensated cirrhosis
Harvoni[42] (ledipasvir/sofosbuvir)	1, 4, 5, 6	Headache, fatigue, asthenia	Coadministration with amiodarone or P-gp inducers	12–24	93–98	Used with ribavirin in cirrhosis or treatment, experienced
Sovaldi[43] (sofosbuvir)	1, 2, 3, 4	Fatigue, headache	Coadministration with amiodarone	24	80–94	Used with ribavirin or IFN
Olysio[44] (simeprevir)	1	Headache, fatigue, nausea, photosensitivity/rash	Coadministration with amiodarone or P-gp inducers	12–24	90–96	Used with sofosbuvir or ribavirin/IFN

Abbreviations: OATP, Organic Anion Transporting Polypeptides; P-gp, P glycoprotein.
[a] Medications listed in order of approval to market (newest to oldest).
[b] Strong inducers of CYP3A include phenytoin, carbamazepine, rifampin, St. John's wort.

General Monitoring

It is imperative that providers maintain close patient follow-up when initiating HCV therapy in order to ensure both medication adherence and tolerance. Furthermore, several laboratory tests should be obtained during and after treatment, but specific monitoring will depend on which regimen is chosen.[15] After completing 4 weeks of treatment with a DAA alone, the following laboratory tests should be obtained:

- Complete blood count (CBC)
- Creatinine with estimated glomerular filtration rate
- Hepatic function panel
- HCV RNA quantitative testing (recheck at week 6 if detectable)

If the HCV RNA (viral load) level has increased by >1 log at week 6, the treatment regimen should be discontinued. HCV RNA should also be checked 12 weeks after completing treatment to evaluate for SVR. Additional laboratory tests or monitoring may be needed for each individual agent; please refer to specific medication package inserts for more details. Patients should also be assessed for any ongoing risk factors for HCV reinfection (intravenous or intranasal drug use), hepatic toxicity (alcohol abuse), and risk of hepatitis B virus reactivation (if patient had positive hepatitis B virus core antibody).

Following treatment, even with obtainment of SVR, those with severe fibrosis (METAVIR F3-F4) or clinical cirrhosis require ongoing surveillance for both HCC and esophageal varices. Ongoing surveillance is achieved with liver ultrasound every 6 months and routine endoscopy, respectively. Serum alpha-fetoprotein lacks sensitivity and specificity as a screening test and is not recommended for HCC surveillance.[45]

Finally, all patients who fail to achieve SVR should be monitored with CBC, comprehensive metabolic panel, and international normalized ratio every 6 to 12 months and should be considered for re-treatment as new options become available.

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